## REMARKS

Applicants thank the Examiner for review of the instant application. For the reasons stated below, the rejections of the presently pending claims are respectfully traversed. Claims 1-5 are presented for examination.

**Rejection Under 37 CFR §§1.821-1.825**

The PTO states that the application fails to comply with the sequence listing requirements because the application does not contain a paper copy of the sequence listing. Applicants submit herewith a paper copy of the sequence listing as requested.

**Rejection Under 35 U.S.C. §101**

The PTO maintains its rejection of pending Claims 1-5 under 35 U.S.C. § 101 as lacking utility for the reasons set forth in the previous Office Actions. The PTO has recognized that the specification discloses that the PRO1357 polynucleotide is more highly expressed in normal stomach and lung tissue compared to stomach and lung tumor tissue, respectively. However, the PTO rejects Applicants' asserted utility, holding that the relationship between mRNA levels and levels of the encoded polypeptide is unpredictable. *Office Action* dated June 27, 2006 at page 4.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the PTO has not met its burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However even if the PTO has met its initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

**Substantial Utility**

*Summary of Applicants' Arguments and the PTO's Response*

Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1357 polypeptide is expressed at least two-fold higher in normal stomach and lung tissues compared to stomach and lung tumor tissue, respectively;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* a decrease, generally leads to a corresponding change in the level of the encoded protein, *e.g.* a decrease;

3. Given Applicants' evidence that the mRNA for the PRO1357 polypeptide is differentially expressed in stomach and lung tumors compared to normal stomach and lung tissue, respectively, it is more likely than not that the PRO1357 polypeptide is also differentially expressed in stomach and lung tumors compared to normal stomach and lung tissue, respectively, making the claimed antibodies useful as diagnostic tools, alone or in combination with other diagnostic tools.

Applicants understand the PTO to be making two arguments in response to Applicants' asserted utility:

1. The PTO challenges the reliability of the evidence reported in Example 18, stating that since the specification does not disclose that PRO1357 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples, the skilled artisan would not reasonably expect that PRO1357 polypeptide could be used as a cancer diagnostic, citing Hu *et al.* (J. Proteome Res., (2003) 2(4):405-12) for support;

2. The PTO cites Haynes *et al.* (Electrophoresis, (1998) 19(11):1862-71), Gygi *et al.* (Mol. and Cell. Bio., (1999) 19(3):1720-30), Genes VI, (Benjamin Lewin, Genes VI (1997), pp. 847-848); Fessler *et al.* (J. Biol. Chem. (2002) 277:31291-31302); Greenbaum *et al.* (Genome Biology, (2003) 4:117.1-117.8); Lian *et al.* (Blood, (2001) 98: 513-524); and Anderson *et al.*, (1997) 18:533-537) as supporting its position that "some references demonstrate a positive correlation between mRNA expression and protein levels, while some show no correlation. From this, one of ordinary skill in the art would not assume that if an mRNA were differentially expressed, the protein would also be expressed in a corresponding manner." *Office Action* at 7.

Applicants respectfully submit that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

*The PTO has Concluded that the data in Example 18 are Sufficient to Establish the Utility of the Claimed Invention*

As an initial matter, Applicants point out that in other applications filed by Applicants that rely on *data from the exact same disclosure, Example 18*, and in which the Applicants have submitted *substantially the same references* in support of their asserted utility, the PTO has concluded that: "[b]ased on the totality of evidence of record, **one of skill in the art would find it more likely than not that an increase in message as measured by RTPCR would be predictive of an increase in protein expression levels,** absent evidence to the contrary. Therefore, the data presented in Example 18, which demonstrates differential expression of nucleic acids encoding PRO1180, also supports a conclusion of differential expression of PRO1180 polypeptide. Therefore, one of ordinary skill in the art would be able to use the PRO1180 polypeptide diagnostically for distinguishing normal kidney and rectal tumor tissues compared to kidney tumor and normal rectal tissue, as asserted by Applicant." See *Examiners Reasons for Allowance* in pending Application No. 10/063,529. See also *Examiners Reasons for Allowance* in Application No. 10/063,530, No. 10/063,524, No. 10/063,582, and No. 10/063,583, all of which conclude that the data presented in Example 18, which demonstrate differential expression of the nucleic acids encoding certain PRO polypeptides, also support a conclusion of differential expression of the PRO polypeptides, making the claimed antibodies that bind the PRO polypeptides useful for diagnostic purposes.

Applicants therefore request that the Examiner recognize the utility of the claimed invention, supported by the data presented in Example 18 and the numerous cited references, as was done in the other applications referenced above.

*The PTO Fails to satisfy its Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"*

In explaining the basis for rejecting the claims as lacking utility, the PTO states:

> Therefore, the fundamental question is, does the data obtained from Example 18 in the specification measuring cDNA levels provide utility for the claimed

PRO1357 polypeptide? Applicants' arguments have been fully considered but are not found persuasive. *Office Action* at 4.

In contrast to the implication by the statement made in the Office Action, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence.

Therefore, the fundamental question is not the adequacy of Applicants' disclosure. Instead, the fundamental question is whether or not the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the asserted utility. For the reasons provided below, Applicants submit that this initial burden has not been met.

Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection was sustained because the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**." M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading textbooks in the field, and is supported by numerous references and the declarations of skilled experts.

Applicants' asserted utility is based on the assertion that changes in mRNA level generally result in corresponding changes in the level of the encoded protein. In rejecting this conclusion, the PTO has cited references by Hu *et al.*, Haynes *et al.*, Gygi *et al.*, Genes VI, Greenbaum *et al.*, Anderson *et al.*, Lian *et al*, and Fessler *et al.* As detailed below, these references are largely irrelevant to the question of whether Applicants' asserted utility is more likely than not true, and several of the references support Applicants' assertions. Given the lack

of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. Furthermore, even if the PTO has met that burden, the Applicants' supporting rebuttal evidence, including three uncontested expert declarations, excerpts from three textbooks, and over 115 scientific articles, is more than sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed antibodies can be used as diagnostic tools for cancer, particularly lung and stomach tumor.

*The PTO's Legal Standard for Substantial Utility is Inconsistent with PTO Policy and the Courts*

In support of the rejection of the claims as lacking a substantial utility, the PTO points to Applicants first Polakis declaration for support of the utility rejection. This declaration teaches that in approximately 80% of observations, changes in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells were compared with their corresponding normal cells. Applicants have previously asserted that the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration is sufficient to show that there is a reasonable correlation between changes in mRNA levels and the levels of the encoded protein. In contrast, the PTO views the Polakis Declaration as supporting the holding of a lack of utility:

> Further based on the Polakis declaration, it is disclosed that in approximately 20% of the observations an increases [*sic*] in the level of a particular mRNA does not correlate with changes in the level of protein expressed from that mRNA. Therefore, further experimentation is required to confirm if the expression of PRO1357 nucleic acid results in increased levels of the encoded protein. *Office Action* at 8-9.

In addition, regarding Applicants data in Example 18, the PTO asserts:

> The art echoes the same sentiments that predictions of functionality based on Example 18 are not iron clad, in many cases overexpression of a specific nucleic acid cannot be associated with cancer. ... The references cited in this Office Action supplement Examiners arguments that predicting function based on the data in Example 18 has flaws and will undermine the accuracy of the conclusions. *Office Action* at 9.

Thus, the PTO implies the following argument: (1) there are exceptions to the general rule that increased mRNA levels correspond to increased levels of the encoded polypeptide; (2)

because such exceptions exist, further experimentation is required to confirm differential expression of PRO1357 polypeptide; and (3) the evidence of record demonstrates that the data of Example 18 "are not iron clad" and have "flaws" that "will undermine the accuracy of the conclusions."

However, the PTO fails to acknowledge that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." *In Re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Contrary to the PTO's assertions in the Office Action, there is no requirement that utility be flawless:

> Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. See, e.g., *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility. *M.P.E.P.* 2107.01 IB.
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> Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965) ... Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* 2107.02 VII (emphasis in original).

It is established that indirect evidence that is reasonably indicative of utility is sufficient to fulfill the requirements of 35 U.S.C. §101. *Nelson v. Bowler*, 626 F.2d 853, 856. Furthermore, there is no requirement that indirect evidence necessarily and always prove actual utility. Instead, there only need be a reasonable correlation between the indirect evidence and the asserted utility. *Id.* at 857, *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051. The indirect evidence need not absolutely prove the asserted utility. All that is required is that the tests be reasonably indicative of the asserted utility. In other words, there need only be a sufficient correlation between the indirect evidence and the utility so as to convince those skilled in the art, to a

reasonable probability, that the novel compound will possess the asserted utility. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564.

Therefore, insofar as the PTO is requiring that Applicants supply direct evidence and/or statistical analysis of their results in order to establish the utility of the claimed subject matter, the PTO's requirements are improper. Furthermore, insofar as the PTO is requiring indirect evidence to necessarily and always prove actual utility, the PTO's requirements also are improper. Instead, the PTO should consider evidence sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true.

*Arguments that it would Require Undue Experimentation to Determine the Utility of the Claimed Antibodies Are Inconsistent with 35 U.S.C. §101*

The PTO provides arguments that it would require undue experimentation to determine the utility of the claimed antibodies. *Office Action* at 10-12. The PTO discusses numerous "Wands Factors" to support its assertions. However, determination of utility under 35 U.S.C. §101 is conducted according to a standard different from a determination of how to use claimed subject matter without undue experimentation under 35 U.S.C. §112, first paragraph:

> The requirement of 35 U.S.C. 112, first paragraph as to how to use the invention is different from the utility requirement of 35 U.S.C. 101. The requirement of 35 U.S.C. 101 is that some specific, substantial, and credible use be set forth for the invention. On the other hand, 35 U.S.C. 112, first paragraph requires an indication of how the use (required by 35 U.S.C. 101) can be carried out, i.e., how the invention can be used. *M.P.E.P.* 2164.07.

Accordingly, insofar as the PTO's "Wands Factors" analysis and assertions of undue experimentation to determine utility of the claimed antibodies are provided to support a holding for lack of utility under 35 U.S.C. §101, this rejection is improper. In the separate section below directed to the rejection under 35 U.S.C. §112, first paragraph, Applicants address the applicability of these arguments to the PTO's enablement rejection.

*The Data Reporting Differential Expression of PRO1357 mRNA are Sufficient to Provide Utility for the mRNA as a Diagnostic Tool*

Applicants turn to the PTO's argument that the evidence of differential expression of the gene encoding the PRO1357 polypeptide in normal stomach and lung tissue compared to stomach and lung tumor, respectively, is insufficient, in view of the teachings of Hu *et al.*

Applicants have previously demonstrated that Hu is not relevant to Applicants' asserted utility by showing that (1) the PTO has recognized that the teachings in the specification of differential expression of the PRO1357 mRNA are sufficient to establish a utility for SEQ ID NO:77, which encodes the PRO1357 polypeptide ("it is agreed that the polynucleotide of SEQ ID NO:77 has this specific utility." *Office Action* dated June 22, 2005, at page 10); and (2) Hu's statements regarding microarray studies are not relevant to the instant application which does not rely on microarray data.

The PTO addresses Applicants' arguments by stating:

> Applicants argue that Hu et al does not show a lack of correlation between mRNA and protein expression. This has been fully considered but is not found to be persuasive. The asserted utility for the polypeptide is based on the presumption that increased mRNA production leads to increased protein production. Hu et al. is directly on point by showing that the presumption is incorrect when designating proteins as diagnostic markers for cancer. *Office Action* at 6.

The PTO points to no teaching in Hu relevant to "the presumption that increased mRNA production leads to increased protein production." Moreover, nothing in Hu even remotely addresses this issue. Hu describes literature mining of expression data and published role of differentially expressed genes in disease. Hu is silent regarding the relationship between changes in mRNA expression and protein levels. Insofar as the PTO has concerns regarding the reliability of Applicants' evidence in Example 18 in view of Hu, this issue has been resolved in the closely related application Serial No. 10/063,711, where this evidence was found to be sufficient to establish the utility of the nucleotide encoding the PRO1357 polypeptide. Thus, this concern is now moot. Insofar as the PTO has concerns regarding the relationship between mRNA and polypeptide levels, Hu is silent in this regard, and, thus, is irrelevant to this question.

In conclusion, Applicants submit that the evidence reported in Example 18 establishes that there is at least a two-fold difference in PRO1357 mRNA in normal stomach and lung tissue

compared to stomach and lung tumor, respectively. The PTO has accepted that the data in Example 18 are sufficient to establish utility for the nucleic acids encoding the PRO1357 polypeptide as diagnostic tools, and therefore any challenge to the sufficiency of the data with respect to the utility of the nucleic acid is inappropriate. Therefore, the only issue which remains is whether the data in Example 18 regarding differential expression of the PRO1357 mRNA are reasonably correlated with differential expression of the PRO1357 polypeptide such that the claimed antibodies have utility as diagnostic tools as well. The teachings of Hu are irrelevant to this question. Therefore, Hu provides no basis to further the PTO's initial burden of offering evidence that one of ordinary skill in the art would reasonably doubt the asserted utility.

*The PTO's Evidence does not Support the PTO's Position tha a Change in mRNA Level for a Particular Gene does not lead to Corresponding Change in the Level of the Encoded Protein*

Applicants turn next to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1357 polypeptide in stomach and lung tumors compared to normal stomach and normal lung, respectively, it is likely that the PRO1357 polypeptide is also differentially expressed; and proteins differentially expressed in certain tumors have utility as diagnostic tools.

In response to Applicants' assertion, the PTO has cited Haynes *et al.* (Electrophoresis, (1998) 19(11):1862-71), Gygi *et al.* (Mol. and Cell. Bio., (1999) 19(3):1720-30), Genes VI, (Benjamin Lewin, (1997), pp. 847-848); Fessler *et al.* (J. Biol. Chem. (2002) 277:31291-31302); Greenbaum *et al.* (Genome Biology, (2003) 4:117.1-117.8); Lian *et al.* (Blood, (2001) 98: 513-524); and Anderson *et al.*, (1997) 18:533-537) as supporting its position that "some references demonstrate a positive correlation between mRNA expression and protein levels, while some show no correlation. From this, one of ordinary skill in the art would not assume that if an mRNA were differentially expressed, the protein would also be expressed in a corresponding manner." *Office Action* at 7.

As Applicants explain below, the only teachings of relevance in these cited references fully support Applicants' assertions. Accordingly, these references are insufficient to meet the

PTO's initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement.

The PTO cites Haynes *et al.* (Electrophoresis, (1998) 19(11):1862-71) and Gygi *et al.* (Mol. and Cell. Bio., (1999) 19(3):1720-30) as providing a low correlation coefficient between mRNA and protein. *Office Action* at 14.

Applicants have previously discussed at length why the Haynes and Gygi references are not relevant to the issue of whether changes in mRNA level for a particular gene lead to changes in protein level. Applicants incorporate by reference the previous arguments, and will not repeat them here.

However, in an attempt to illustrate why references which relate to static levels of mRNA and protein across different genes are not relevant to Applicants' asserted utility, Applicants provide the following. Haynes and Gygi attempted to discover a single numerical ratio common between all steady state mRNA levels and all steady state protein levels. The data of Haynes and Gygi indicated that the steady state ratio of mRNA level:protein level varied for different genes, and hence no single numerical ratio existed. Based on this, the references concluded that protein levels cannot be accurately calculated from mRNA levels, and that "it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification." *Haynes* at 1863, right column, full paragraph 2.

In contrast, Applicants' assertions require no knowledge of a ratio between mRNA levels and protein levels, nor do Applicants' assertions require calculation of protein levels based on measured mRNA levels. Applicants simply assert that a change in mRNA level for a particular gene typically leads to a corresponding change in the encoded protein level. *See, e.g., First Grimaldi Declaration* at paragraph 7. Haynes and Gygi were concerned with a different question, and, therefore, none of the data or conclusions of these references has any bearing on Applicants' assertions.

To exemplify the difference between these references and Applicants' asserted utilities, Applicants offer the following illustration and analogy with the understanding that like all illustrations and analogies, they are not perfect and therefore do not represent any admissions or binding statements regarding Applicants' disclosure or invention.

Haynes and Gygi discuss whether there is a single numerical value that describes the relationship between the static level of mRNAs and proteins, *i.e.* across different genes. This is equivalent to conducting a hypothetical Experiment 1, where a particular cell type has 100 copies of mRNA for gene X, 200 copies of mRNA for gene Y, and 400 copies of mRNA for gene Z. If there is a single numerical correlation between static mRNA levels and protein levels across genes, the ratio of the amount of proteins X:Y:Z would be approximately 1:2:4. This is essentially what the cited references examined.

In contrast, Applicants are relying on a correlation between changes in mRNA level for a particular gene leading to a corresponding change in the level of the encoded protein. For example, in hypothetical Experiment 2, if gene X has 100 copies of mRNA per cell in condition A (*e.g.* normal), and 200 copies of mRNA for gene X in condition B (*e.g.* tumor), the amount of protein X in condition A would be smaller than the amount of protein X in condition B, for example, having a ratio of 1:2, such that there is a correlation between the change in the level of mRNA and the change in the level of protein for a particular gene.

The PTO argues that because there is no correlation between static levels of mRNA and protein across genes, as illustrated by Experiment 1, one of skill in the art would not expect an increase or decrease in the amount of mRNA for a particular gene to result in a corresponding change in the amount of the encoded protein, as illustrated in Experiment 2. This is simply wrong – there does not need to be a single numerical ratio across genes for there to be a correlation in changes for a particular gene.

Applicants emphasize, and the PTO will recognize, that these are simplified illustrations to demonstrate the difference between the two issues being examined. However, these illustrations make clear that <u>even if</u> there is no correlation in the first experiment looking at static levels of mRNA and protein across genes, there can still be a correlation between changes in mRNA and protein for a particular gene as examined in the second experiment.

In response to Applicants' statements, the PTO argues:

> As to correlation of an individual gene, Gygi et al. and Haynes et al. point to a great unpredictability about expression of a nucleic acid and its encoded protein. Predicting a correlation for any single gene is more difficult than for a large pool of genes showing a general trend. This can be seen by the low 0.356 correlation coefficient described above by Haynes et al. Each point in the figures of Haynes et al. and Gygi et al. are individual genes (see Fig. 1 and Figs. 5-6, respectively).

> Therefore, the authors did examine single genes. Haynes et al. supports the rejections of record and also says that the results are expected to be representative for mammalian cells (*e.g.*, like the human cell from which the PRO1357 nucleic acid was isolated). *Office Action* at 14-15.

Thus, while the PTO acknowledges that "[e]ach point … are [*sic*] individual genes," the PTO asserts that "[p]redicting a correlation for any single gene is more difficult than for a large pool of genes showing a general trend." It is not mathematically possible to "predict a correlation" when only a single data point is used. As acknowledged by the PTO, Haynes' Figure 1 depicts a single data point per gene. It would not have been mathematically possible for Haynes to examine the correlation of protein levels with mRNA levels for any particular gene because only a single data point was used per gene. Accordingly, it is not possible for Haynes' data to have any bearing on Applicants' assertions that a change in the level of an mRNA typically leads to a corresponding change in the level of the encoded protein. As such, nothing in Haynes or Gygi supports the PTO's initial burden of offering evidence that one of ordinary skill in the art would reasonably doubt the asserted utility.

The PTO newly cites Anderson et al. as suggesting a poor correlation between mRNA expression and protein expression. The teachings of Anderson do not support the rejection of the claimed antibodies as lacking utility. Applicants have asserted that generally an increase or decrease (*i.e.*, change) in mRNA levels for the same gene leads to a respective increase or decrease (*i.e.*, change) for the corresponding polypeptide. Anderson compared mRNA abundance of 19 genes versus protein abundance in human liver samples. As with Haynes and Gygi, Anderson never compared different mRNA levels of the same gene versus protein levels. Anderson is completely silent regarding changes in mRNA levels or changes in polypeptide levels for the same gene. Accordingly, the results of Anderson are not relevant to Applicants' assertions regarding the relationship between changes in mRNA levels and the corresponding polypeptide levels. As such, Anderson cannot support the PTO's initial burden of offering evidence that one of ordinary skill in the art would reasonably doubt the asserted utility.

The PTO points to Genes VI, (Benjamin Lewin, Genes VI (1997), pp. 847-848) as teaching that "control of gene expression can occur at multiple stages and that production of RNA cannot inevitably be equated with the production of protein." *Office Action* at 5. However, the PTO's selective reading of Genes VI ignores the remainder of the sentence: "having

acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription" (emphasis added). Thus, the PTO chooses to focus on the minority of gene regulatory events and ignore the teachings of the "overwhelming majority" of protein production regulatory events which occur at the transcription level. A fair and even interpretation of this reference strongly supports Applicants' assertions and weighs against the PTO's initial burden of offering evidence that one of ordinary skill in the art would reasonably doubt the asserted utility.

The PTO newly cites Greenbaum et al. ("Comparing protein abundance and mRNA expression levels on a genomic scale," *Genome Biology*, 4:117.1-117.8 (2003)) for the proposition that there is no significant correlation between mRNA and protein levels. The PTO points to Greenbaum's summary of four studies comparing mRNA and protein levels, and statement that these studies "have reported only minimal and/or limited correlation." *Greenbaum* at 117.3, right column.

Like Haynes, Gygi and Anderson, Greenbaum does not provide any support for the PTO's position because the authors examined the correlation between mRNA level and protein level by examining levels across different genes. Applicants have explained above why such measurements are not relevant to Applicants' assertions. As for the references discussed by Greenbaum in the portion of the paper cited by the PTO (page 117.3, second column and page 117.04, first column), Greenbaum cites three references which allegedly found a poor or no correlation: Anderson and Seilhamer (Electrophoresis 1997; 18:533-537); Lichtinghagen *et al.* (European Urology 2002; 42:398-406); and Chen *et al.* (Mol. and Cell. Proteomics 2002; 1:304-313). In addition, Greenbaum reports a fourth reference which found a strong correlation: Orntoft *et al.* (Mol. Cell. Proteomics. 2002; 1(1):37-45). The three references cited by Greenbaum are not contrary to Applicants' assertion, the fourth reference supports Applicants' position, and therefore Greenbaum does not offer the PTO any support for its rejection.

Applicants have addressed the Anderson reference above, and have explained why it is not relevant. Briefly stated, the authors conducted a study that looked at static levels of mRNA and protein across different genes. For the reasons discussed above, a lack of correlation between static levels of mRNA and protein across different genes is not relevant to Applicants'

assertions, and therefore Greenbaums' statements based on these experiments are irrelevant and do not support the PTO's rejection.

The second reference cited by Greenbaum is Lichtinghagen *et al.*, stating that the reference shows no significant relationship between mRNA and protein for matrix metalloproteinases (MMPs 2 and 9) and the tissue inhibitor of metalloproteinase 1 (TIMP-1) in human prostate cancer. Lichtinghagen examined the level of MMP-2, MMP-9 and TIMP-1 in cancerous and non-cancerous parts of 17 human prostate samples at both the mRNA and protein level. The level of mRNA was determined using RT-PCR, and the level of protein was determined using quantitative zymography and ELISA. Lichtinghagen reports that comparing non-cancerous to cancerous tissue, mRNA levels were decreased for MMP-2, and unchanged for MMP-9 and TIMP-1. *See Lichtinghagen* at Abstract (attached as Exhibit 1). In contrast, looking at the protein level, MMP-2 levels were unchanged, while MMP-9 expression was higher and TIMP-1 levels were lower. *Id.* Thus, Lichtinghagen reports that there was no correlation between mRNA levels and protein levels. *Id.*

First, it is important to note that of the three genes examined, only one (MMP-2) showed any change in mRNA expression levels between cancerous and non-cancerous tissues. While statistically significant, the change was small (approximately 33% decrease), far less than a two-fold change. It is therefore not surprising that the authors did not see a measurable change in the amount of MMP-2 protein.

For MMP-9 and TIMP-1, the authors report that there was no change in the level of mRNA, but there was a change in protein level. This apparent lack of correlation between mRNA and protein levels is not contrary to Applicants' assertion that a change in mRNA level generally leads to a change in protein level. Applicants are not attempting to predict the level of mRNA based on changes in protein level, and Applicants have not asserted that the only means for changing the level of protein is to change the amount of the encoding mRNA. Therefore a change in protein without a change in mRNA is not contrary to Applicants' assertions.

Second, the authors in Lichtinghagen note that in another study, researchers found a direct correlation between mRNA levels and protein levels for MMP-2 in prostate cancer. *See Lichtinghagen* at 403, col. 2, *citing* Stearns and Wang (Cancer Res. 1993; 53(4):878-83). In the Stearns and Wang reference cited in Lichtinghagen, the authors report differences in MMP-2

mRNA levels between cancerous, benign and normal stromal tissue from human prostate. The authors state that "[e]nzyme-linked immunosorbent assays demonstrated that the amounts of type IV collangenase protein [MMP-2 protein] correlated directly with the mRNA levels in the tumor tissue." *Stearns and Wang* at Abstract (abstract attached hereto as Exhibit 2). Therefore, contrary to the results reported in Lichtinghagen, at least one other study reports a good correlation between changes in mRNA and protein levels for MMP-2 in prostate cancer.

In conclusion, Lichtinghagen is not contrary to Applicants' assertion that generally, a change in mRNA level leads to a corresponding change in protein level. Lichtinghagen reported a single gene where an apparent change in mRNA did not result in a corresponding change in the level of protein. However, the change in mRNA level was very small, and other researchers have reported a direct correlation between mRNA levels and protein levels for the same gene in human prostate samples. The two other genes examined by Lichtinghagen did not show a change in mRNA level, and therefore say nothing about Applicants' assertion. Therefore, Greenbaum's statements based on Lichtinghagen do not support the PTO's rejection.

The third reference cited by Greenbaum is Chen, *et al.* As an initial matter, it is important to note that a portion of Chen is not relevant to Applicants' assertion that changes in the level of mRNA lead to changes in the level of the encoded polypeptide. In one experiment similar to that of Haynes, Chen examined the global relationship between mRNA and the corresponding protein abundance by calculating the average mRNA and protein level of all the samples for each gene or protein, and then looked for a correlation across different genes. Based on these data, Chen reported that "no significant correlation between mRNA and protein expression was found ($r = -0.025$) if the average levels of mRNA or protein among all samples were applied across the 165 protein spots (98 genes)." *Chen* at Abstract. This measurement of a correlation across <u>different</u> genes is not relevant to Applicants' asserted utility for the same reasons discussed above with respect to the Haynes *et al.* reference.

Chen also looked at the level of mRNA of 98 individual genes and their corresponding proteins across the samples. Chen reports that 17% (28 of 165) of the protein spots, or 21.4% (21 of 98) of the genes, showed a statistically significant correlation between protein and mRNA expression. *Chen* at Abstract.

However, read in its entirety, Chen provides scant evidence to counter Applicants' asserted utility because portions of Chen support Applicants' assertions, and the remaining portions provide little insight into the relationship between changes in mRNA levels and changes in the corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells.

Applicants have asserted that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. The data in Chen support Applicants' assertion. In Figures 2A-2C, Chen plots mRNA value vs. protein value for three genes. In these figures, a wide range of mRNA expression levels were observed (approximately seven- to eight-fold), and a correlation between mRNA and protein levels was observed for all three mRNA/protein pairs. This supports Applicants' assertion that there is a correlation between changes in mRNA levels which are two-fold or greater and changes in polypeptide expression.

Chen also reports a lack of correlation for some mRNA/protein pairs to support his assertion that polypeptide levels cannot be accurately predicted from mRNA levels. However, as is explained below, the apparent lack of a correlation cannot be used as evidence that Applicants' assertion of a general correlation is wrong.

To determine if there is a correlation between changes in mRNA and changes in protein levels, one would have to conduct experiments where a measurable change in mRNA for a particular gene is observed, and then examine if there was a corresponding change in the level of the corresponding protein. Stated differently, if there is no substantial change in mRNA levels for a particular gene, one cannot measure a correlation between changes in mRNA and changes in the encoded protein for that gene. Therefore, one must know if the individual genes studied by Chen were differentially expressed to know if the observed lack of correlation has any relevance to Applicants' assertions of a general correlation between changes in mRNA and protein.

Applicants have provided in Example 18 disclosure of differential expression of mRNA encoding the PRO1357 polypeptide in stomach and lung tumors. Applicants have submitted that one skilled in the art would recognize that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. Thus, Applicants submit that one skilled in the art, based on Applicants' disclosure of differential expression of

PRO1357 mRNA, would believe that the PRO1357 polypeptide is likely to also be differentially expressed. Applicants make no assertions regarding expected changes in protein levels when mRNA levels are unchanged, and evidence of protein levels when mRNA levels are unchanged has no relevance to Applicants' assertion. Importantly, unlike Applicants, Chen did not examine differences in mRNA between tumor and normal tissue where one would expect to find substantial changes in the level of mRNA for certain genes. Instead, Chen merely selected proteins whose identity could be determined regardless of any changes in expression level. Chen at 306, right column. Therefore, it is not known if there was any substantial difference in mRNA levels for the various studied genes across samples – in short, with the exception of the genes in Figures 2A-2C, it is not known if the genes examined were differentially expressed.

Also of significance for Applicants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis. Since almost all samples tested by Chen were from the same type of tissue, one would expect most genes examined by Chen to have similar mRNA or protein levels across the samples. In the absence of substantial differential expression, no correlation would be observed. Because it is not known if there was a change in the level of the genes studied by Chen, *i.e.* whether they were differentially expressed, the lack of an observed correlation cannot be used to counter Applicants' assertion.

In sum, the only data reported by Chen shows substantial changes in the expression of mRNA, Figures 2A-C, which confirms Applicants' assertion that substantial changes in mRNA levels (e.g., 2-fold or greater) will correspond to substantial changes in polypeptide expression. Further, these data explain the lack of observed correlation between mRNA levels and protein levels for other genes reported by Chen – there is no indication the genes are differentially expressed. Thus, Chen's results do not refute Applicants' position. Instead, Chen supports Applicants' position that a significant correlation between changes in mRNA and protein levels exists for changes in mRNA levels that are 2-fold or greater.

In further support of Applicants' position, Chen cites Celis *et al.* (FEBS Lett., 480:2-16 (2000)) stating that the authors "found a good correlation between transcript and protein levels among 40 well resolved, abundant proteins using a proteomic and microarray study of bladder

cancer." *Chen* at 311, first column (emphasis added). As mentioned above, the lack of a correlation across genes is not relevant to Applicants' asserted utility, and therefore Chen's discussion of this issue as interpreted by Greenbaum offers no support for the PTO's position.

Given the fact that portions of Chen as well as the relevant references cited by Chen support Applicants' position, and the remainder of Chen cannot be relied on as contrary to the Applicants' position, the teachings of Greenbaum in regard to Chen are not contrary to Applicants' asserted utility. Thus, Greenbaum's teachings in view of Chen are not contrary to Applicants' assertion, and therefore Greenbaum's reliance on Chen cannot support the PTO's rejection.

In contrast to these three references which offer no or very little support for the PTO's position, Greenbaum also cites a reference by Ornoft *et al.* Applicants have previously discussed Ornoft in detail. Briefly stated, the authors found that "[i]n general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations. Only one gene showed disagreement between transcript alteration and protein alteration." *Id.* at 42, col. 2. The alternations in mRNA and protein included both increases and decreases. *Id.* at 43, Table II. Clearly, a correlation in 39 of 40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in protein level.

Thus, when considered as a whole, the references cited by Greenbaum actually support Applicants position since the three which report no correlation are either irrelevant or offer no or little support for the PTO's position, and the one which reports a correlation between changes in gene expression and protein expression reports a correlation for 39 out of 40 genes studied.

Finally, Applicants note that to the extent that the PTO insists on relying on references such as Haynes, Gygi and Anderson where mRNA/protein relationships are examined across different genes, Greenbaum clearly undercuts the PTO's position that there is no correlation between mRNA and protein levels as applied to Applicants' data. When Greenbaum analyzed differentially expressed mRNAs, the authors found a significant correlation between mRNA and protein levels across different genes. The authors state:

> [W]e looked at correlations between mRNA and protein abundance for those ORFs that had varied or steady levels of mRNA expression over the course of the cell cycle. ... Logically, we would assume that those ORFs that show a large degree of variation in their expression are controlled at the transcriptional level – the variability of the mRNA expression is indicative of the cell controlling mRNA

> expression at different points of the cell cycle to achieve the resulting and desired protein levels. Thus we would expect, and we found, a high degree of correlation (r=0.89) between the reference mRNA and protein levels for these particular ORFs; the cell has already put significant energy into dictating the final level of protein through tightly controlling the mRNA expression, and we assume that there would then be minimal control at the protein level. *Greenbaum* at 117.4, last paragraph, to 117.5, paragraph spanning left and right columns.

This clearly supports Applicants, not the PTO, since Applicants' data and declarations show that the PRO1357 mRNA was differentially expressed by at least two-fold. Applicants emphasize that studies examining a global relationship between mRNA and protein across genes are not relevant to Applicants' assertions. However, to the extent that the PTO disagrees and continues to rely on Haynes, Gygi and Anderson, Greenbaum teaches that one of skill in the art would expect a correlation between mRNA and protein levels across different genes for genes which are differentially expressed. Thus, based on the PTO's own flawed reasoning, Greenbaum clearly supports Applicants' assertions.

In conclusion, nothing in Greenbaum is contrary to Applicants' assertion. The one reference relied on by Greenbaum which is most relevant (Orntoft *et al.*) actually supports Applicants' assertion, and Greenbaum's analysis of differentially expressed genes significantly undercuts the PTO's position based on Haynes, Gygi and Anderson, since Greenbaum found a high degree of correlation between mRNA levels and protein levels for differentially expressed genes.

The PTO newly cites Lian *et al.* as showing a poor correlation between mRNA expression and protein abundance. *Office Action* at 8.

In Lian, the authors looked at the mRNA and protein levels of genes in a derived promyelocytic mouse cell-line during differentiation of the cells from a promyelocytic stage of development to mature neutrophils following treatment with retinoic acid. *Lian* at Abstract. The level of mRNA expression was measured using 3'-end differential display (DD) and oligonucleotide chip array hybridization, and protein levels were qualitatively assessed following 2-dimensional gel electrophoresis. *Id.* at Abstract, Table 6.

Lian *et al.* used DD and array hybridization to examine the expression of genes 0, 24, 48 and 72 hours after treatment with retinoic acid. *Id.* at 515, col. 1, ¶ 2. Using this information, the authors constructed a database of mRNA level changes during differentiation of the cell line. *Id.*

at 518, col. 2, ¶ 2. Lian *et al.* also examined protein expression at 0 and 72 hours after retinoic acid treatment. Lian reports that they were able to identify 28 proteins which they considered differentially expressed. *Id.* at 521, Fig. 5. Of those 28, only 18 had corresponding gene expression information in the database, and only 13 had measurable levels of mRNA expression. *Id.* at 521, Table 6. The authors then compared the qualitative protein level from the 2-D electrophoresis gel to the corresponding mRNA level, and reported that only 4 genes of the 18 present in the database had expression levels which were consistent with protein levels. *Id.* at 521, col. 1. The authors note that "[n]one of these was on the list of genes that were differentially expressed significantly (5-fold or greater change by array or 2-fold or greater change by DD)." *Id.* at 521, bridge paragraph (emphasis added). Based on these data, the authors conclude "[f]or protein levels based on estimated intensity of Coomassie dye staining in 2DE, there was poor correlation between changes in mRNA levels and estimated protein levels." *Id.* at 522, col. 2, ¶ 2.

These results are not contrary to Applicants' assertion. Applicants emphasize that Applicants are asserting that a measurable change in mRNA level generally leads to a corresponding change in the level of protein expression, not that changes in protein level can be used to predict changes in mRNA level. Based on the authors' criteria, mRNA levels were significantly changed if they were at least 5-fold different when measured using a microchip array, or 2-fold different when using the more sensitive 3'-end differential display (DD). Of the 28 proteins listed in Table 6, only one has an mRNA level measured by microarray which is differentially expressed according to the authors (spot 7: melanoma X-actin, which mRNA changed from 2539 to 341.3, and protein changed from 1 to 3). None of the other mRNAs listed in Table 6 show a significant change in expression level when using the criteria established by the authors for the less sensitive microarray technique.

There is also one gene in Table 6 whose expression was measured by the more sensitive technique of DD, and its level increased from a qualitative value of 0 to 2, a more than 2-fold increase (spot 2: actin, gamma, cytoplasmic). This increase in mRNA was accompanied by a corresponding increase in protein level, from 3 to 6.

Therefore, although the authors characterize the mRNA and protein levels as having a "poor correlation," this does not reflect a lack of a correlation between a change in mRNA level

and a corresponding change in protein level. Only two genes meet the authors' criteria for differentially expressed mRNA level, and of those, one apparently shows a corresponding change in protein level and one does not. *Id.* at 521, Table 6. Thus, there is little basis for the authors' conclusion relied on by the PTO that "it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels." *Office Action* at 8 (emphasis added).

PTO also has cited Fessler *et al.* to support the assertion that there is no significant correlation between mRNA and protein expression. Fessler is not contrary to Applicants' asserted utility, and actually supports Applicants' assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. Applicants make no assertions regarding changes in protein levels when mRNA levels are unchanged, nor does evidence of changes in protein levels when mRNA levels are unchanged have any relevance to Applicants' asserted utility.

Fessler *et al.* studied changes in neutrophil (PMN) gene transcription and protein expression following lipoplysaccharide (LPS) exposure. Fessler lists in Table VIII a comparison of the change in the level of mRNA for 13 up-regulated proteins and 5 down-regulated proteins. Of the 13 up-regulated proteins, a change in mRNA levels is reported for only 3 such proteins. For these 3, mRNA levels are increased in 2 and decreased in the third. Of the 5 down-regulated proteins, a change in mRNA is reported for 3 such proteins. In all 3, mRNA levels also are decreased. Thus, in 5 of the 6 cases for which a change in mRNA levels are reported, the change in the level of mRNA corresponds to the change in the level of the protein. This is consistent with Applicants' assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein.

Regarding the remainder of the proteins listed in Table VIII, in 6 instances, protein levels changed while mRNA levels were unchanged. This evidence has no relevance to Applicants' assertion that changes in mRNA levels lead to corresponding changes in protein levels, since Applicants are not asserting that changes in mRNA levels are the only cause of changes in protein levels. In the final 6 instances listed in Table VIII, protein levels changed while mRNA was noted as "absent." This evidence also has no relevance to Applicants' assertion that changes in mRNA levels causes corresponding changes in protein levels. By virtue of being "absent," it is not possible to tell whether mRNA levels were increased, decreased or remained unchanged in

PMN upon contact with LPS. Nothing in these results by Fessler suggests that a change in the level of mRNA for a particular protein does not generally lead to a corresponding change in the level of the encoded protein. Accordingly, these results are not contrary to Applicants' assertions.

The PTO points to Fessler's statement regarding Table VIII that "a poor correlation was also found between corresponding transcripts and proteins." *Examiner's Answer* at 6. As is clear from the above discussion, this statement does not relate to a lack of correlation between a change in mRNA levels leading to a change in protein levels, because in 5 of 6 such instances, changes in mRNA and protein levels correlated well. Instead, this statement relates to observations in which protein levels changed when mRNA was either unchanged or "absent." As such, this statement is an observation that in addition to transcriptional activity, LPS also has post-transcriptional and possibly post-translational activity that affect protein levels, an observation which is not contrary to Applicants' assertions. Accordingly, Fessler's results are consistent with Applicants' assertion that a change in mRNA level of for a particular protein generally leads to a corresponding change in the level of the encoded protein, since 5 of 6 genes demonstrated such a correlation. As such, Fessler's results are consistent with Applicants' assertions and do not support the PTO's burden to provide evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility.

In conclusion, of the references cited by the PTO, Haynes *et al.*, Gygi *et al.*, Lian *et al.*, and Anderson *et al.* do not provide any basis to call into question Applicants assertions that changes in mRNA typically lead to corresponding changes in the encoded protein. Accordingly, these references are insufficient for the PTO to meet its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. Moreover, the Genes VI, Greenbaum *et al.* and Fessler *et al.* references cited by the PTO support Applicants assertions, and not the PTO's position. As such, the evidence of record is clear that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement.

*Previously Submitted Exhibits 2-13 Are Relevant to the PTO's Argument Against Allowance of the Claims*

Applicants submit that even if the PTO has met its initial burden, which it has not, Applicants have provided overwhelming evidence supporting Applicants assertion that changes in mRNA typically lead to corresponding changes in the encoded protein. Applicants previously submitted Exhibits 2-13, comprising 81 references, in support of their argument for the correlation between mRNA levels and protein levels. The references of Exhibits 2-13 provide strong evidence supporting the Applicants' position. The PTO has responded to this evidence by stating:

> In their response Applicants have provided 156 references some directly related to establishing a link between mRNA levels to protein expression, and some not. The office has supplied a sampling of references that show that there is unpredictability in establishing a link between an increase in mRNA levels and the corresponding increase in the encoded polypeptide. ... The only conclusion that can be reached based on the conflicting literature is that we have confusion and unpredictability and we cannot say that an increase in cellular PRO1357 mRNA levels results in an increase in cellular levels of PRO1357 polypeptide. The Office could also provide, if not 159 references as supplied by Applicants, a very high number arguing away from a correlation between mRNA and protein, but that would be futile. Does the one that supplies the most references wins? The point is the art provides data supporting both arguments. *Office Action* at 4-5.

Applicants submit that the present issues under examination do not constitute a contest, but instead a determination of patentability based on the totality of the record. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); *In re Corkill*, 771 F.2d 1496, 1500, 226 USPQ 1005, 1008 (Fed. Cir. 1985); M.P.E.P. §§2107 II and 2107.02VI. The totality of the record as it stands is clear: one skilled in the art would reasonably believe that changes in mRNA levels typically lead to corresponding changes in the levels of the encoded protein. There is no basis in PTO policy or the standards set by the courts for the PTO to ignore evidence submitted by Applicants or for the PTO to make an adverse conclusion on the utility of claims based on less than the totality of the evidence. Accordingly, Applicants respectfully request that the PTO consider references of Exhibits 2-13 in its evaluation of the utility of the claimed subject matter.

In addition to the previously submitted references, Applicants have previously submitted the Polakis Declaration in support of their position that in general, differential mRNA levels correlate with differential protein levels. Applicants submit herewith as Exhibit 3 a second Declaration by Dr. Polakis (Polakis II) that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (i.e., greater than 90%)

that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions.

Applicants further submit herewith a copy of a declaration by Randy Scott, Ph.D. (attached as Exhibit 4). Dr. Scott is an independent expert in the field of molecular diagnostics, with over 15 years experience. He is the author of over 40 scientific publications in the fields of protein biology, gene discovery, and cancer, and is an inventor on several issued patents. His curriculum vitae is attached to the declaration. In paragraph 10 of his declaration, Dr. Scott states:

> One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression levels. *Scott Declaration* at ¶10 (emphasis added).

Applicants submit the opinion of yet another expert in the field that differential mRNA levels for a particular protein in a given tissue generally lead to corresponding differential levels of the encoded protein. Importantly, Dr. Scott also states that, contrary to the contentions of the PTO, diagnostic markers can be identified "without the need to directly measure individual protein expression levels." This opinion is supported by Dr. Scott's extensive experience in the field, as well as the fact that an entire industry has developed around technology to assess differential mRNA expression. As stated previously, there would be little reason to study differential mRNA expression levels if those differences did not result in corresponding differential encoded protein levels.

The case law has clearly established that in considering affidavit evidence, the PTO must consider all of the evidence of record anew. *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143

(C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996)(quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner." *Id.* at 1583. Applicants also respectfully draw the PTO's attention to the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Part IIB, 66 Fed. Reg. 1098 (2001).

**Utility – Conclusion**

Applicants remind the PTO that the evidence supporting utility does not need to be direct evidence, nor does it need to provide an exact correlation between the submitted evidence and the asserted utility. Instead, evidence which is "reasonably" correlated with the asserted utility is sufficient. *See Fujikawa*, 93 F.3d at 1565 ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); *Cross*, 753 F.2d at 1050 (same); *Nelson*, 626 F.2d at 857 (same). In addition, utility need only be shown to be "more likely than not true." *M.P.E.P.* at § 2107.02, part VII (2004). Considering the evidence as a whole in light of the relevant standards for establishing utility, Applicants have established at least one specific, substantial, and credible utility. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

**Rejections under 35 U.S.C. § 112, first paragraph – Enablement**

The PTO also maintains its rejection of pending Claims 1-5 under 35 U.S.C. §112, first paragraph, arguing that because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility, one skilled in the art would not know how to use the claimed invention. *See Office Action* at 2. For the reasons provided above, Applicants

submit that Applicants have established at least one specific, substantial, and credible utility, and the PTO's rejection of Claims 1-5 under 35 U.S.C. § 112, first paragraph, as lacking utility should be reversed.

In addition, the PTO states that the claims lack enablement because it would require undue experimentation to determine the utility of the claimed antibodies. *See Office Action* at 3 and 10-13. The PTO further provides a "Wands factors" analysis based on reasoning and evidence already used in asserting that the claims lack utility: the protein did not have an art-recognized use, there is evidence that nucleic acid expression does not correlate with protein expression, and the specification does not provide sufficient experimental details. The arguments directed toward lack of enablement are interspersed with and based on the same reasoning as the arguments directed toward lack of utility. *See Id.* at 10-13. Moreover, the enablement rejection asserts that it would require undue experimentation to determine the utility of the claimed antibodies:

> Were PRO1357 differentially expressed and were this expression significant, repeatable and the information sufficiently complete to allow use of the polypeptide without undue experimentation, it would have utility as a diagnostic tool. It, however, has none of these necessities. *Office Action* at 11.

Thus, the PTO demonstrates that the enablement rejection is based on lack of utility grounds. If the enablement rejection were to be based on grounds other than lack of utility, the rejections should have been imposed separately according to the M.P.E.P., which admonishes:

> To avoid confusion during examination, any rejection under 35 U.S.C. 112, first paragraph, based on grounds other than "lack of utility" should be imposed separately from any rejection imposed due to "lack of utility" under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph. *M.P.E.P.* § 2107.01 IV.

The PTO did not separate the enablement rejection from the utility rejection. This is clear from the assertions of the PTO:

> The issue in this application is the insufficiency of disclosure to support a specific and substantial or well established utility or to allow the skilled artisan to use the claimed invention without undue experimentation. *Office Action* at 11.
>
> ***

> The conclusionary statement of Grimaldi of the necessary existence of an at least two-fold differentiation in nucleic acid expression does not support a utility for or enable the invention ... *Office Action* at 12.
>
> ***
>
> Therefore, even accepting Dr. Grimaldi's opinion (see first paragraph of p. 13 of response), the declaration is insufficient to overcome the rejections of the claims under 35 USC 101 or 112 first paragraph, for the reasons discussed above. *Office Action* at 13.

Accordingly, the PTO makes clear in the Office Action that the rejection under 35 U.S.C. 112, first paragraph, is intertwined with, and coextensive with, the "lack of utility" rejection under 35 U.S.C. 101. Any rejection under 35 U.S.C. 112, first paragraph, based on grounds other than "lack of utility" would have been imposed separately from any rejection imposed due to "lack of utility" under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph in accordance with M.P.E.P. § 2107.01 IV.

Furthermore, the PTO's "Wands factors" analysis is not based on any argument or evidence not similarly asserted by the Examiner in holding that the claims lack utility. While Applicants acknowledge that claims can be rejected as drawn to subject matter having utility while nevertheless lacking enablement, in the instant case, the PTO provides no reasoning and submits no evidence to support holding that the claims lack enablement that differs from the reasoning and evidence provided for holding that the claims lack utility. Thus, by repeating the same arguments and relying on the same evidence for both the utility and enablement rejections, the PTO demonstrates that the enablement rejection is grounded on a "lack of utility" basis. As such, the Examiner's "Wands factors" analysis is grounded on a "lack of utility" basis. Accordingly, the Examiner's enablement rejection is only proper if the utility rejection is proper. Applicants have argued above that one skilled in the art would have believed the claimed antibodies have a substantial, specific and credible utility, and, thus, a utility rejection for the claimed antibodies is not proper. Applicants further submit that because a utility rejection for the claimed antibodies is not proper, the Examiner's enablement rejection of the claimed antibodies also is not proper.

Even if the PTO's enablement rejection extended beyond the utility rejection, which it does not, Applicants submit that the specification enables one skilled in the art to make and use

the full scope of the claims without undue experimentation. The claimed subject matter relates to antibodies to polypeptide of SEQ ID NO: 78. The specification discloses how to make the claimed antibodies, for example in paragraphs [0365]-[0374] and Example 10. Similar methods also were known in the art. In addition, the specification discloses that the claimed antibodies can be used in diagnostic assays to detect the expression of PRO1357 in specific types of tissue. *See e.g., Specification* at ¶[0407]. In light of the differential expression of the nucleic acid encoding the PRO1357 polypeptide in lung and stomach tumors compared to normal lung and stomach, respectively, one of skill in the art would have expected the PRO1357 polypeptide to be differentially expressed in these tumors as well. Therefore, given the teaching in the specification on how to make and use the claimed antibodies to detect expression of PRO1357 polypeptide in specific tissues, one of skill in the art would have been enabled to practice the claimed invention without undue experimentation.

Because Applicants' specification teaches how to make and use the claimed subject matter, it must be taken as being in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the statements contained therein which are relied on for enabling support. *See M.P.E.P.* § 2164.04. It is incumbent for the PTO "to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *Id.* (quoting *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). This can be done "by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact." *Id.*

The PTO refers only once to evidence, stating that "there is evidence in the prior art that even for those nucleic acids differentially expressed in tumors, a correlated expression for the encoded protein is not a given." *Office Action* at 10. Applicants have submitted in regard to the above utility rejection that the PTO's position is inconsistent with the knowledge in the art as a whole. Accordingly, the PTO has cited no evidence that supports the enablement rejection. As such, the PTO has not provided a reason to doubt the objective truth of the statements contained in the specification which are relied on for enabling support.

In conclusion, in the PTO's entire analysis of the Wands factors, the PTO points only once to evidence. Applicants have submitted overwhelming evidence demonstrating that the

PTO's evidence is inconsistent with the knowledge in the art as a whole. Moreover, the PTO has not submitted any evidence demonstrating that one skilled in the art could not use the teachings of the specification to make the claimed antibodies and use them in diagnostic assays to detect the expression of PRO1357 in specific types of tissue.

The PTO merely provides unsubstantiated arguments that the specification is insufficient because various experimental specifics were not provided in the specification, and without disclosing such specifics, it would require undue experimentation to use the claimed antibodies. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.P.E.P.* § 2164.01; *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). *See also In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (CCPA 1976). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404, citing *In re Jackson*, 217 U.S.P.Q. 804, 807-808 (Bd. App. 1982). Based on the teachings of the specification and the level of skill in the art, it was routine to make and use the claimed antibodies, in diagnostic assays for the PRO1357 polypeptide. No undue experimentation was required for a Ph.D. scientist with several years of experience to use these routine methods, in view of the teachings in the specification, in order to determine details such as the binding properties of the generated antibodies, the ability of an antibody to bind to a sample, or specific details of sample binding. Accordingly, it would not have required undue experimentation for one skilled in the art to make and use the claimed antibodies. The claimed invention is, therefore, fully enabled. Moreover, the PTO provides no evidence to support an assertion that, absent various specific experimental details, it would require undue experimentation to use the claimed antibodies. Absent such evidence, there is no reasonable basis to question the sufficiency of the disclosure.

In view of the above, Applicants submit that the specification, in view of the knowledge in the art, fully enabled the use of the claimed antibodies. The PTO has provided no significant evidence or argument to the contrary. In view of the above, Applicants request that the PTO reconsider and withdraw its rejection under 35 U.S.C. § 112, first paragraph.

**Rejection Under 35 U.S.C. §102(b)**

Claims 1-5 are rejected as anticipated under 35 U.S.C. § 102(b) over WO 01/16318 (published March 8, 2001) or WO 00/12708 (published March 9, 2000).

The PTO asserts that "[b]ecause the claims do not meet the requirements of 35 U.S.C. § 112, first paragraph, ... and the earlier application[s] likewise do not meet those requirements, the instant application does not receive the benefit of priority to earlier filed applications." *Office Action* at page 25.

Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. The preliminary amendment states that the instant "application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to U.S. Provisional Application 60/099741 filed 9/10/1998."

The sequences of SEQ ID NOs: 77 and 78 were first disclosed in U.S. Provisional Application 60/099,741 filed 9/10/1998 in Figures 1 and 2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed antibodies, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Applicants submit that, in view of the arguments above, the claimed antibodies have utility and are fully supported by the specification in accordance with 35 U.S.C. § 112, first paragraph. Moreover, Applicants submit that the previously filed applications, to which Applicants have properly claimed priority, also support the claimed antibodies. Even if it were to

be determined that Applicants are not entitled to their earliest priority date, the entire subject matter of the present application was disclosed in, and therefore is entitled to the priority date of, PCT Application PCT/US00/23328 filed August 24, 2000. Accordingly Applicants are entitled to a priority date no later than August 24, 2000.

WO 01/16318 was published March 8, 2001. Thus, WO 01/16318 was not published more than one year prior to Applicants' priority date, as required under 35 U.S.C. § 102(b). Accordingly, WO 01/16318 cannot be prior art under 35 U.S.C. § 102(b).

Similarly, WO 00/12708 was published March 9, 2000. Thus, WO 00/12708 was not published more than one year prior to Applicants' priority date, as required under 35 U.S.C. § 102(b). Accordingly, WO 00/12708 cannot be prior art under 35 U.S.C. § 102(b).

In view of the above, Applicants respectfully request withdrawal of this rejection of the claims.

## CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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